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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/888,639	06/26/2001	Randolph J. Noelle	P 0280639	9079

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EXAMINER	
GAMBEL, PHILLIP	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 07/01/2003

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)
	09/888639	NOBLE
	Examiner	Art Unit
	GAMBEL	1644

– The MAILING DATE of this communication appears on the cover sheet with the correspondence address –

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☑ Responsive to communication(s) filed on 4/14/03

2a)☑ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☑ Claim(s) _____ is/are pending in the application. 1, 4-15, 17-50

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☑ Claim(s) _____ is/are rejected. 1, 4-15, 17-50

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☑ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☑ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☑ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4)☐ Interview Summary (PTO-413) Paper No(s). _____.
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other:

PAPER NO. 9

DETAILED ACTION

1. Applicant's amendment, filed 4/14/03 (Paper No. 7), has been entered.
Claims 2-3 and 16 have been canceled.
Claims 1, 4-5, 12, 15, 17-18, 27, 30 and 41-42 have been amended.

Given applicant's amendment to recite only the elected species anti-gp39 antibodies, claims 1, 4-15 and 17-50 are under consideration in the instant application.

2. The text of those sections of Title 35 USC not included in this Action can be found in a prior Action.
This Office Action will be in response to applicant's arguments, filed 4/14/03 (Paper No. 7).
The rejections of record can be found in the previous Office Action (Paper No. 6).

3. Upon reconsideration of applicant's amendment, filed 4/14/03 (Paper No. 7), the previous rejections under 35 U.S.C. 112, first and second paragraphs, with respect to the MR1 antibody /hybridoma have been withdrawn.

4. Given applicant's amendment to recite only the elected species anti-gp39 antibodies, the previous rejections under 35 USC § 112, first paragraph, "written description" and scope of enablement have been withdrawn with respect the recitation "antagonist of the receptor on the surface of the T cell which inhibits the interaction of the ligand with the receptor" or "a gp39 antagonist".

5. Claims 1, 4-15 and 17-50 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention essentially for the reasons of record set forth in Paper No. 6

Applicant has not disclosed how to use gp39-specific antagonists in combination with antigen-presenting cells (APC) to induce antigen-specific T cell tolerance therapeutically for the antigens and species encompassed by the claimed methods. There is insufficient information or nexus with respect to the in vivo ability of gp39-specific antagonists and APC to accomplish the claimed therapeutic endpoint of immunological tolerance.

Applicant's arguments, filed 4/14/03 (Paper No. 7), have been fully considered but are not found convincing with respect to tolerance induction in humans essentially for the reasons of record.

Applicant argues that the difficulty alleged by Auchincloss does not refute success in inducing tolerance in humans accomplished by other researches, citing various references in support.

In contrast to applicant's assertions, Xu et al. (J. Immunol., 170: 2776-2782, 2003) discloses that anti-CD154 (anti-CD40L, anti-gp39) antibodies variably prolong allograft survival in nonhuman primates and that an immunosuppressive drug such as rapamycin improves the efficacy of anti-CD154 antibody (See Abstract).

The following of record is reiterated herein for applicant's convenience.

In vitro and animal model studies have not correlated well with in vivo clinical trial results in patients. Since the therapeutic indices of biopharmaceutical drugs and particularly tolerance induction can be species- and model-dependent, it is not clear that reliance on the limited in vivo experimental models accurately reflects the relative efficacy of the claimed tolerance induction regimens.

In agreement with the art-known experience; Noelle et al. (U.S. Patent No. 5,876,718) discloses that anti-gp39 may have different effects being used and the method of presentation (see column 24, lines 3-5). Although gp39-specific antibodies have been able to induce some immunosuppression in certain murine strain combinations, it is not clear that a state of immunological tolerance has been achieved or simply immunosuppression. More importantly, it is not clear that the skilled artisan would extrapolate the ability to induce immunological tolerance from these limited murine experimental results to the breadth of targeted antigens including alloantigens encompassed by the claimed invention.

It is not clear that the instant murine experimental transplantation systems provide the strong histocompatibility antigenic barriers associated with the therapeutic targets encompassed by the claimed therapeutic strategies for inducing tolerance (rather than immunosuppression). A problem with murine systems is the ease with rejection can be suppressed.

Tolerance is the long-lasting nonreactivity of the immune system to a specific set for antigens, maintained without on-going immunosuppression. Many different strategies have been developed to achieve transplantation tolerance some have which led to indefinite graft survival in rodents, none of these strategies have yet been applied to human patients in a way that allows reliable withdrawal or exogenous immunosuppression. Auchincloss (chapter 11 in Transplantation Immunology, Bach and Auchincloss Eds. Wiley-Liss, New York, 1995, pages 211-218, see page 211). While tolerance inducing strategies that have worked well in rodents, such strategies have been much less successful even when tested in nonhuman primates and other large animals. Also, the Conclusion on page 217 states that Although more than a dozen different techniques to induce tolerance in rodents are now available, the fact remains that none of them has been used successfully in the clinic. Inducing transplantation tolerance in human must therefore be very hard to do. And that reading of this chapter should be wary of simple solution to this complex approaches

In view of the lack of predictability of the art to which the invention pertains the lack of established clinical protocols for effective tolerance-induction therapies, undue experimentation would be required to practice the claimed therapeutic in vivo methods with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the claimed in vivo methods and absent working examples providing evidence which is reasonably predictive that the claimed methods are effective for inducing antigen-specific T cell tolerance.

Applicant's arguments are not found convincing as the claims read on inducing T cell tolerance in humans, if the intent of these claims are to read on true tolerance versus the induction of antigen-specific nonresponsiveness.

6. Claims 1, 4, 5, 7-15 and 17, 18, 20-32, 34-44 and 46-50 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Lederman et al. (U.S. Patent No. 6,403,091) in view of Berschorner (U.S. Patent No. 5,597,563) and Cobbold et al. (U.S. Patent No. 6,056,956) essentially for the reasons of record set forth in Paper No. 6.

Applicant's arguments, filed 4/14/03 (Paper No. 7), have been fully considered but are not found convincing essentially for the reasons of record set forth in the previous Office Action (Paper No. 6).

Despite the general recognition of a need to promote graft acceptance and survival, applicant argues that there is insufficient specific teaching, suggestion or motivation in the prior art to arrive at the claimed invention.

While applicant acknowledges that Lederman et al. teach the use of 5C8-specific (CD40L-specific) antibodies to inhibit the rejection of transplanted tissues, applicant argues that Lederman et al. do no describe the induction of tolerance nor nonreactivity in the absence of continued immunosuppression.

While applicant acknowledges that Berschorner describes methods of inducing antigen-specific immune tolerance by providing APCs in combination with an immunosuppressant, applicant argues that Berschorner does not teach the use of an anti-gp39 antibody.

While applicant acknowledges that Cobbold teach methods of inducing tolerance induction using an antigen and an immunosuppressant with CD4- / CD8-specific antibodies, applicant argues that Cobbold et al. do not teach the use of anti-gp39 (anti-CD40L) antibody.

Once a prima facie case of obviousness has been made the burden of going further is shifted to applicant. In re Keller, 642 F.2d 4B, 208 USPQ 871, 882 (CCPA 1981). This applicant has not done, but rather argues the references individually and not their combination. One cannot show non-obviousness by attacking references individually where the rejections are based on a combination of references. In re Young 403 F.2d 759, 150 USPQ 725 (CCPA 1968). See MPEP 2145.

Further, it is noted that the claimed methods recite "comprising" which leaves the claim open for the inclusion of unspecified ingredients even in major amounts. See MPEP 2111.03.

In contrast to applicant's arguments and assertions, the combination of the prior art teachings provide sufficient motivation and expectation of success in targeting T cells and inducing antigen-specific nonresponsiveness or tolerance in promoting long-term graft survival at the time the invention was made for the reasons of record reiterated herein for applicant's convenience.

Lederman et al. teach the use of 5C8-specific / CD40L-specific antibodies, including chimeric and humanized antibodies (see columns 7-8) to inhibit the immune response, including methods of inhibiting the rejection of transplanted tissues, including heart, kidney and liver (see column 11, paragraph 6) as well as to treat diabetes (see column 11, paragraph 7) (see entire document).

Lederman et al. differs from the claimed invention by not disclosing the use of an additional allogeneic or xenogeneic cell in transplanting tissues and organs of interest.

It is noted that the allogeneic or xenogeneic cells employed in the instant methods are an additional element(s) with respect to the transplanted tissue or organ per se. For example, transplanted tissues and/or organs, including the bone marrow would comprise allogeneic or xenogeneic cells; but these types of transplanted tissues and organs do not appear to be the substance of the instant claimed methods.

Berschorner teach methods of inducing antigen-specific immune tolerance by providing antigen presenting cells containing the antigen to which specific tolerance is desired (see entire document, including Background of the Invention, including column 2, paragraph 2, Detailed Description of the Invention). Berschorner also teach that the antigen presenting cells, which can be isolated from a number of hemopoietic tissues and can include dendritic cells, Langerhans cells and mononuclear phagocytes (e.g., see column 6, paragraphs 3-4) would be administered with an immunosuppressant agent contemporaneously with the antigen presenting cells (see Detailed Description of the Invention, including column 8, column 4). Both alloantigens and xenoantigens are targeted (see columns 5, paragraph 4 - column 6, paragraph 1), including the treatment of a number of diseases (see column 6, paragraph 2).

Cobbold et al. teach methods of preventing graft rejection in tissue and organ transplants with anti-T cell antibodies in order to induce tolerance by providing antigen (see entire document, including columns 1-4). Cobbold et al. teach the provision of the antigen and the immunosuppressant at different times to provide an tolerance-permissive environment (see column 1-4).

In contrast to applicant's assertions and given the teachings of providing antigen and/or antigen presenting cells containing the antigen to which specific tolerance is desired, including those at the time transplant, contemporaneously with immunosuppressants, as taught by Berschorner and/or Cobbold; one of ordinary skill in the art would have been motivated to combine the immunosuppressive properties of the CD40L-specific antibodies, taught by Lederman et al., to create an environment conducive to tolerance or specific unresponsiveness in the transplantation of a number of tissues and organs at the time the invention was made.

In contrast to applicant's assertions and given the teachings of Cobbold et al. that the presence of antigen as well as the use of anti-T cell antibodies can provide an environment conducive to tolerance or specific unresponsiveness, one of ordinary skill in the art would have had a reasonable expectation of success and motivation to employ the CD40L-specific antibodies in combining antigen presenting cells in transplanting a variety of tissues and organs at the time the invention was made.

Given the prior art teachings of inducing nonresponsiveness to both alloantigens and xenoantigens as well as the use of a variety of antigen presenting cells to a variety of transplanted tissues and organs, one of ordinary skill in the art would have employed a variety of antigen presenting cells, including those encompassed by the instant claims as known antigen presenting cells, particularly the ready availability of human B cells as antigen presenting cells at the time the invention was made. Also, transplanting a number of tissues and cells, including those encompassed by the instant claims was known and practiced by the ordinary artisan at the time the invention was made.

In contrast to applicant's arguments, the prior art provides sufficient teachings, motivation and expectation of success in targeting the same T cells with the same gp39- / CD40L-/5C8- specific antibodies and antigen presenting cells to achieve the same long term graft survival in the same transplant patients at the time the invention was made.

It would have obvious to a person of ordinary skill in the art at the time the invention was made to apply the teachings of Berschorner AND/OR Cobbold et al. to those of Lederman et al. to provide methods of providing an environment conducive to tolerance or specific unresponsiveness by combining an immunosuppressant such as the CD40L-specific antibodies, taught by Lederman et al. with a source of alloantigen or xenoantigen, as taught by Berschorner and Cobbold et al. To transplant a variety of tissues and cells. A person of ordinary skill in the art would have been motivated to produce this resultant therapeutic regimen to provide an environment conducive to tolerance or specific unresponsiveness to decrease the rejection of the transplanted tissue or organ and to increase the survival of such transplants. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Applicant's arguments are not found persuasive.

15. Claims 1-21, 24-35 and 38-50 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over
claims 1-34 of U.S. Patent No. 5,683,693,
claims 1-34 of U.S. Patent No. 5,902,585, and
claims 1-7 of U.S. Patent No. 6,375,950

Although the conflicting claims are not identical, they are not patentably distinct from each other because the pending claims and the patented claims appear to read on the same or nearly the same methods of inducing specific unresponsiveness. Further, the patented claims appear to anticipate the instant methods.

Claims 1-21, 24-35 and 38-50 are directed to an invention not patentably distinct from claims 1-34 of commonly assigned U.S. Patent No. 5,683,693 and claims 1-34 of commonly assigned U.S. Patent No. 5,902,585 for the reasons set forth above.

The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP § 2302). Commonly assigned U.S. Patent No. 5,683,693 and U.S. Patent No. 5,902,585, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee is required under 37 CFR 1.78© and 35 U.S.C. 132 to either show that the conflicting inventions were commonly owned at the time the invention in this application was made or to name the prior inventor of the conflicting subject matter. Failure to comply with this requirement will result in a holding of abandonment of the application.

A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications filed on or after November 29, 1999.

Applicant's amendment, filed 4/1303 (Paper No. 7), indicates that terminal disclaimer will be filed when one or more pending claims are in condition for allowance.

16. No claim allowed.

The method claims drawn to the use of the MR1 antibody appear to be free of the prior art.
It appears that the MR1 bind the mouse CD40L and the 5C8 antibody binds the human CD40L.

17. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (703) 308-3997. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

Phillip Gambel, PhD.
Primary Examiner
Technology Center 1600
June 30, 2003

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